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HOWREY LLP - East
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BORGHEST, CHRISTINA M	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,076	BENGTSSON, BENGT-AKE	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8-15,18,25,28-30,33,36 and 37* is/are pending in the application.

4a) Of the above claim(s) *28-30,36 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-15,18,25 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/2006; 3/2007; 12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-2 (in part), 5-6, 8-13, 14-15 (in part) 18 (in part), 25 (in part), 33 (in part)), directed to a method of administering human growth hormone or human growth hormone releasing hormone, in the reply filed on 30 January 2009 is acknowledged. Claims 28-30, 36 and 37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 30 January 2009.

Claim 1 is amended. Claims 1, 2, 5, 6, 8-15, 18, 25 and 33 are under examination.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 6, 8-15, 18, 25 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) Claim 1 recites a method for the treatment of a Parkinsonism-Plus Syndrome comprising administration of a substance, which is indefinite because there is no step that clearly relates back to the preamble. For example, there is no step indicating that

administration of a substance results in treatment of the Parkinsonism-Plus Syndrome. In addition there is no recitation of a patient population, thus the claims encompass administration of GH for any reason to anybody.

(ii) Claim 1 is indefinite because the elements recited in the claim do not constitute proper Markush groups. The claim is indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

(iii) Claims 11-12 are indefinite because it is not clear what protein variant the claims are referring to. Claims 11-12 depend from claim 1, which recites a method of administering hGH, a hGH variant, hGHRH, a hGHRH variant, or combinations thereof. Thus, it is not clear if claims 11-12, are referring to a hGH variant, a hGHRH variant, or both.

Claims 2, 5, 6, 8-15, 18, 25 and 33 are rejected because they depend from an indefinite claim, and do not remedy the deficiency of claim 1.

Claim Rejections - 35 USC § 112, first paragraph—Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 8, 10-15, 18, 25 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the amelioration of the symptoms of Multiple Symptom Atrophy or MSA comprising administering to a person suffering from MSA a substance selected from the group

consisting of (a) human growth hormone (hGH), (b) a variant of (a) that has at least 70% sequence identity thereto and that has agonistic activity on the hGH receptor, (c) a salt of (a) or (b), wherein administration of said substance ameliorates the symptoms of Multiple Symptom Atrophy or MSA, does not reasonably provide enablement for the claims as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

i) The generic claim (claim 1) is drawn to "prevention" in the alternative. The plain English meaning of the word prevention implies 100% success at stopping an event from occurring. The claimed methods do not achieve this goal. The specification provides only a prophetic example. Furthermore, a recent study by Holmberg et al. (Movement Disorders, 2007; 22: 1138-1144) teach that hGH administration in patients with multiple symptom atrophy, or MSA, might decrease symptoms, although results

were non-significant (see abstract; p. 1142, Figure 1). The results were equivocal, but suggest that GH therapy may ameliorate symptoms of the disease, but does not prevent pathological events from occurring. See p. 1143, right column, 2nd and 3rd paragraphs:

> This study is the first to report the effects of GH treatment of patients with MSA. ***As yet, no drug has been shown to reduce progression of MSA.*** (Emphasis added by Examiner). At the time this study was designed, no reliable data were available on spontaneous evolution in MSA patients of the clinical scales used to assess disease progression. Thus, when designing the study, it was impossible to make a reliable sample size calculation for detection of a positive effect. In addition, 37% of the patients discontinued prematurely during the study owing to the aggressive nature of the underlying disease…The results of this study, therefore, suggest that a larger dose of r-hGH could be tolerated and may be necessary to demonstrate improvements in patients with MSA.

In other words, the study by Holmberg et al. offers the possibility that GH treatment could lessen symptoms associated with MSA, but also underscore the complexity and the amount of further research that is needed to establish how to treat this disease.

The use of the word "prevention" in the claims implies that not a single adverse event occurs, and that is not the case, as can be seen by the teachings of Holmberg and colleagues. In addition, the literature teaches that although Parkinsonism-Plus (also called Parkinsonism) is distinct from Parkinson's Disease, the two share many similarities; see the abstract of Mark M (Neurol Clin. 2001; 19: 607-27), which states:

> "The atypical Parkinsonian or Parkinson Plus syndromes are often difficult to differentiate from Parkinson's disease and each other. In this article, the clinicopathological characteristics of dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and cortical-basal ganglionic degeneration are discussed. These disorders, although clinically distinct, may have more similarities than previously thought."

Furthermore, it is difficult to differentiate clinically between classical Parkinson's disease and Parkinsonism-Plus Syndrome. Although the specification discloses at paragraph [0048] a clonidine diagnostic test known in the art that might be useful for the identification of MSA patients, the literature indicates that the results are equivocal at best. Clarke et al. (Lancet, 1999; 353: 1329-30) teach the following:

> Our inability to show a significant difference in the growth-hormone response to intravenous clonidine in patients with early untreated IPD, late levodopa-treated IPD, and MSA suggests that this test is unlikely to assist in the differentiation of IPD from MSA.

These references underscore the complexity of Parkinsonism Plus Syndrome and the difficulty in distinguishing it from classical Parkinson's disease. With regard to classical Parkinson's disease, the literature clearly states that it cannot be prevented. For instance, see the website downloaded 2 April 2009 from: webmd.com/parkinsons-disease/guide/parkinsons-disease-prevention?print=true, which states "there is no known way to prevent Parkinson's Disease". The prior art is silent with respect to 100% prevention of every pathological event occurring during the course of a disease or disability after administration of a medicament designed to treat that particular disease or disability.

ii) The independent claim recites variants "having agonistic activity" that are encoded by DNA that hybridizes to the complement of DNA encoding GH or human growth hormone releasing hormone (hGHRH) or analogs thereof. Hybridization stringency is defined as the degree to which mismatches are tolerated in a hybridization assay. In a lower stringency assay nucleic acids which diverge significantly would hybridize in the assay. Nevertheless even a higher stringency assay allows for

molecules that contain point mutations, splice sites, frameshift mutations or stop codons which would result in use of a different open reading frame, and thus could encode a protein that differs in structure from GH or hGHRH that would hybridize, thus the phrase "hybridize" significantly broadens the scope of the claim. Given the limited structural requirement recited in the claim in the method step (hybridization) and the requirement that the variant have "agonistic activity", undue experimentation would be required to make and test every possible variation of the invention for its ability to agonize the hGH or hGHRH receptors, and thus treat Parkinsonsism Plus Disorders. Although case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled, the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Ibid.; In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). The specification discloses a number of patents describing substances capable of promoting the release of growth hormone (GHRH—see p. 22, last paragraph through p. 23, 1st paragraph), nevertheless, since the claims require functional activity in the absence of any structural limitation, they require that the person

of skill in the art undergo an undue amount of experimentation to test each possibility for "agonistic activity".

iii) Given the complexity of the art concerning diagnosis and treatment of Parkinsonism Plus Disorders, discussed above and underscored by the teachings of Holmberg et al. (cited above), and that the claims are drawn to treatment of this intractable collection of diseases, it would require undue experimentation from one of skill in the art to make and test every possible variant of hGHRH that might be effective. Neither the specification, nor the literature suggests that hGHRH would be useful for the treatment of Parkinsonism Plus Disorders and a large quantity of experimentation would be required of the skilled artisan to determine such. Such experimentation is considered undue. The limited guidance in the specification is not adequate and is merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

Due to the large quantity of experimentation necessary to make and test all claimed embodiments that hybridize to complement of DNA encoding hGH or hGHRH for "agonistic activity" and the ability to treat and prevent Parkinsonism Plus Disorders, the lack of direction/guidance presented in the specification regarding the same and the absence of working examples directed to the same, the complex nature of the invention ((see discussion above and recited references), (the level of skill of those in the art,) and the breadth of the claims which fail to recite structural limitations whilst requiring "agonistic activity", undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, first paragraph—Written Description

Claims 1, 2, 6, 8, 10-15, 18, 25 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is directed to a method of treatment and/or prevention of Parkinsonism-Plus Syndrome comprising administering to a person in need thereof (a) human growth hormone (hGH) or human growth hormone releasing hormone (hGHRH), (b) a variant of (a) that has at least 70% sequence identity thereto and that has agonistic activity on the hGH or hGHRH receptors, respectively (c) a salt of (a) or (b). The specification discloses treatment with hGH and examples of hGH variants known in the art. In the case of hGHRH variants, the specification discloses patents that disclose hGHRH variants at p. 22, lines 33-36.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a extremely limited partial structure in the form of a recitation of a variant having agonistic activity on the hGH or hGHRH receptors that is encoded by a

DNA sequence that hybridizes to the complement of the native DNA sequence of either hGH or hGHRH. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of (a) human growth hormone (hGH) or human growth hormone releasing hormone (hGHRH), (b) a variant of (a) that has at least 70% sequence identity thereto and that has agonistic activity on the hGH or hGHRH receptors, respectively (c) a salt of (a) or (b), the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising (a) human growth hormone (hGH) or human growth hormone releasing hormone (hGHRH), (b) a variant of (a) that has at least 70% sequence identity thereto and that has agonistic activity on the hGH or hGHRH receptors, respectively (c) a salt of (a) or (b), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 5, 6, 8, 14, 15, 18, 25 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Ng et al. (U.S. Patent No. 5,869,452, issued 9 February 1999—hereafter the '452 patent—on Applicants' 149 form filed 7 November 2006). The '452

patent teaches administration of GH or a variant of GH containing amino acid residues 177-191 for the treatment of obesity (see abstract, claims 1-4), thus meeting the limitations of instant claims 1, 5 and 8. In addition, the '452 patent meets the limitation of instant claim 2, since the instant claims encompass administration of GH to anybody for any reason. Nevertheless, the '452 patent teaches the administration of GH for treatment of obesity (i.e. treatment of disease), thus in no way conflicts with the teachings of the instant specification. They also teach at column 3, lines 34-54 that full length GH is encompassed by the invention as well as:

> homologues, analogues, mutants, variants or derivatives of the native carboxyl-terminal sequences of human growth hormone or growth hormone of other animal species, and which are derived from natural or synthetic (including recombinant) sources, provided always that the resulting peptide retains the biological activity of the native carboxyl-terminal sequence described herein…
>
> These homologues, analogues, mutants, variants or derivatives may be derived by insertion, deletion or substitution of amino acids in, or chemical modification of, the native carboxyl-terminal sequence. Amino acid insertional derivatives include amino and/or carboxylic terminal fusions as well as intra-sequence insertions of single or multiple amino acids. Insertional amino acid sequence variants are those in which one or more amino acid residues are introduced into a predetermined site in the protein although random insertion is also possible with suitable screening of the resulting product. Deletional variants are characterised by the removal of one or more amino acids from the sequence. Substitutional amino acid variants are those in which at least one amino acid residue in the sequence has been replaced by another of the twenty primary protein amino acids, or by a non-protein amino acid. ***Chemical modifications of the native carboxyl-terminal sequence include the acetylation of the amino-terminus and/or amidation of the carboxyl-terminus and/or side chain cyclisation of the native carboxyl-terminal sequence***. (Emphasis added by Examiner to point out claim limitations met).

Thus, this meets the limitations of claims 6, 14, 15 and 25. At column 5, lines 30-32, the '452 patent teaches dose range of 10μg (i.e., 0.01mg) – 20mg of active ingredient.

The range recited in claim 18, (a) is broadened by the term "about", thus 0.01 to 20mg can be reasonably interpreted as being about 0.1 to 10mg. Finally, the '452 patent teaches at column 4, lines 18-19 that the medicament can be delivered using subcutaneous or intramuscular routes, thus meeting the limitation of claim 33.

Claims 1, 2, 5, 6, 8, 10, 11, 12, 13, 15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Bengtsson et al. (U.S. Patent No. 5,736,515; issued 7 April 1998—hereafter the '515 patent—on Applicants' 149 form filed 7 November 2006) as evidenced by Bauman (Endocrine Reviews, 1991; 12: 424-449) and the AACE Growth Hormone Task Force, Endocrine Practice, Jan/Feb 2003; 9: 64-76. The '515 patent teaches administration of growth hormone or GH or analogues thereof in a dosage of 0.1-3 u/kg/week (see for instance, claims 1-8), which meets the limitations of instant claims 1, 5, 6 and 8. Claim 1 of the '515 patent recites "growth hormone or analogues thereof", which meets the limitation of "human growth hormone" or "naturally occurring growth hormone" or a GH which "comprises amino acids 177 to 191 of hGH". In addition, claim 8 of the '515 patent recites "recombinant" growth hormone, which meets the limitation of instant claim 6. Because the instant claims currently encompass administration of GH to anybody for any reason (see Rejections under 35 U.S.C. 112, second paragraph), the '515 patent also meets the limitations of claim 2. Nevertheless, the '515 patent teaches at column 2, lines 7-11 that "the medicament can be for treatment of damages in the brain and for treatment of damages in the memory function of the brain and degenerative disorders of the brain," thus in no

way conflicts with the teachings of the instant specification, but rather teaches administration of the same agent to the same patient population. Regarding claim 10, which recites a GH variant lacking the 15 amino acid residues from Glu32 to Glu46 of hGH, claim 13, which recites a dimer of human GH, and claims 14 and 15, which recite chemically derivatized GH (e.g., deamidated GH), the Examiner used the reference by Bauman to provide evidence that these forms are naturally occurring pituitary GH variants (see p. 428, Table 2; and p. 428, whole page through p. 430, left column; see also p. 432, whole page, under "oligomeric GH", which includes as discussion of naturally occurring non-covalent GH dimers). Regarding claims 11 and 12, which recite GH variants lacking the first 8 or 13 amino acid residues at the N-terminus, the Examiner used the reference by Bauman to provide evidence that there is a GH variant lacking the first 43 amino acids (GH_{44-191}), which is possibly a native form of GH that has potent diabetogenic activity (see p. 430, right column, last paragraph through p. 431, left column, 1st paragraph). Since claim 1 of the '515 patent recites "GH or analogues thereof", these naturally occurring analogues of GH, as evidenced by Bauman, are encompassed by the prior art. The reference by Bauman et al. shows that the characteristic analogues of GH, though not explicitly named by the Bauman reference, are disclosed inherently. Regarding the dosage recited in claim 18, the Examiner used the publication put out by the AACE Growth Hormone Task Force as a lexicon because it provides the definition of the international unit and its conversion factor for converting to mg, as recited in the instant application. At p. 74, left column, last paragraph of the AACE document, it states that:

> Because most of the early studies of GH treatment for GHD in adults were done in Europe, publications cited dosing in IU or mU (international units), and early recommendations were often on a weight-adjusted (IU/kg)…The conversion of IU or mU to mg is 3:1. For example, a mean starting dose of 0.6 IU is equivalent to 0.2 mg/day. Mean maintenance dosages of 0.15 to 0.25 mU/kg per week are equivalent to 0.05 to 0.08 mg/kg per week—which, for a 70-kg man, would be 0.35 to 0.56 mg/day.

Using the conversion factor of 3:1, 0.1-3U/kg/week is equal to 0.03-1mg/kg/week, which divided by 7 is equal to 0.004 – 0.14mg/kg/day and for a 70kg man this is equivalent to 0.28 – 10mg/day. As can be seen from parts (a)-(c), (g)-(j) of instant claim 18, the range taught by the '515 patent falls exactly within the range recited in that claim. Note MPEP 2131.01, which addresses the use of more than one reference in making 35 U.S.C. 102 Rejections:

> A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:
> (A) Prove the primary reference contains an "enabled disclosure;"
> (B) Explain the meaning of a term used in the primary reference; or
> (C) Show that a characteristic not disclosed in the reference is inherent.

In the instant case the reference by the AACE growth task force was used as a lexicon for the definition of IU and its conversion to mg, thus for reasons under (B) and (C). In addition, note that MPEP 2131.01 (III), also states that the critical date of extrinsic evidence showing a universal fact such as conversion of IU to mg need not antedate the filing date.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, 5, 6, 8, 10-15 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Johannsson et al. (U.S. Patent No. 6,846,800; filed 31 March 7 1998—hereafter the '800 patent) as evidenced by Bauman (Endocrine Reviews, 1991; 12: 424-449). The '800 patent teaches administration of growth hormone or GH or analogues thereof in a dosage of 9.5μk/kg/day (see for instance, claims 1-4), which meets the limitations of instant claims 1, 5, 6 and 8. Claim 1 of the '800 patent recites "growth hormone or analogues thereof", which meets the limitation of "human growth hormone" or "naturally occurring growth hormone" or a GH which "comprises amino acids 177 to 191 of hGH". In addition, claim 3 of the '800 patent recites "recombinant" growth hormone, which meets the limitation of instant claim 6. Regarding claim 10, which recites a GH variant lacking the 15 amino acid residues from Glu32 to Glu46 of hGH, claim 13, which recites a dimer of human GH, and claims 14 and 15, which recite chemically derivatized GH (e.g., deamidated GH), the Examiner used the reference by Bauman to provide evidence that these forms are naturally occurring pituitary GH variants (see p. 428, Table 2; and p. 428, whole page through p. 430, left column; see also p. 432, whole page, under "oligomeric GH", which includes as discussion of naturally occurring non-covalent GH dimers). Regarding claims 11 and 12, which recite GH variants lacking the first 8 or 13 amino acid residues at the N-terminus, the Examiner used the reference by Bauman to provide evidence that there is a GH variant

lacking the first 43 amino acids (GH_{44-191}), which is possibly a native form of GH that has potent diabetogenic activity (see p. 430, right column, last paragraph through p. 431, left column, 1st paragraph). Since claim 1 of the '800 patent recites "GH or a functional analog thereof", these naturally occurring analogues of GH, as evidenced by Bauman, are encompassed by the prior art. The reference by Bauman et al. shows that the characteristic analogues of GH, though not explicitly named by the Bauman reference, are disclosed inherently. Because the instant claims currently encompass administration of GH to anybody for any reason (see Rejections under 35 U.S.C. 112, second paragraph), the '800 patent also meets the limitations of claim 2. Nevertheless, claim 1 of the '800 patent recites the treatment of metabolic syndrome (i.e., method of treating disease), thus in no way conflicts with the teachings of the instant specification (also at column 2, lines 19-29). Regarding the dosage recited in instant claim 18, claim 4 of the '800 patent recites a dosage of 9.5μk/kg/day, which divided by 1000 (for conversion to mg) and multiplying by 70 (average number of kg of a man) works out to 0.665mg/day, which falls within the range recited in instant claim 18 (see especially parts (a)-(c)).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ng et al. (U.S. Patent No. 5,869,452) as applied to claims 1, 2, 5, 6, 8, 14, 15, 18, 25 and 33 above and further in view of Goeddel et al. (Nature, 1979; 281: 544-548—on Applicants 1449 form filed 7 November 2006). The first factor to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. The teachings of the '452 patent and how they meet the limitations of claims 1, 2, 5, 6, 8, 14, 15, 18, 25 and 33 is discussed above and applicable here, and is hereby incorporated. The second factor is to ascertain the differences between the prior art and the instant claims. The '452 patent do not explicitly teach the methionyl GH. Goeddel et al. show how to make methionyl GH (see whole document; also Figure 1 at p. 545). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '452 patent by making methionyl GH, as taught in Goeddel et al. because Goeddel et al. teach that "using a novel combination of chemically synthesized DNA and cDNA, a recombinant E. coli strain has been constructed which produces hGH in large amounts" (see p. 548, right column, last

paragraph). Furthermore, the claims of the '452 patent encompass administration of GH analogues and recombinant GH. The person of ordinary skill in the art would have been motivated to make methionyl hGH because Goeddel et al. teach that their recombinant hGH "compares favorably with the expression levels of other cloned genes using the same promoter in optimized conditions" and furthermore that it was produced in large amounts (see p. 548, right column, last 2 paragraphs). For this reason as well, the person of ordinary skill in the art could have reasonably expected success. The teachings of Goeddel et al. indicate that the level of ordinary skill in the art of recombinant production of hGH was high. Furthermore, the instant specification does not contain any objective evidence indicating that methionyl hGH has any surprising qualities with respect to the treatment of MSA. Thus claim 9 does not contribute anything non-obvious over the prior art.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bengtsson et al (U.S. Patent No. 5,736,515—cited above) as evidenced by Bauman (cited above) and the AACE Growth Hormone Task Force (cited above) as applied to claims 1, 2, 5, 6, 8, 10, 11, 12, 13, 15 and 18 above and further in view of Goeddel et al. (Nature, 1979; 281: 544-548—on Applicants 1449 form filed 7 November 2006). The first factor to consider when making a rejection under 35 U.S.C. 103(a) is to determine the scope and contents of the prior art. The teachings of the '515 patent and how they meet the limitations of claims 1, 2, 5, 6, 8, 10, 11, 12, 13, 15 and 18 as evidence by Bauman and the AACE Growth Hormone Task Force is discussed above and applicable

here, and is hereby incorporated. The second factor is to ascertain the differences between the prior art and the instant claims. The '515 patent does not explicitly teach the methionyl GH. Goeddel et al. show how to make methionyl GH (see whole document; also Figure 1 at p. 545). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '515 patent by making methionyl GH, as taught in Goeddel et al. because Goeddel et al. teach that "using a novel combination of chemically synthesized DNA and cDNA, a recombinant E. coli strain has been constructed which produces hGH in large amounts" (see p. 548, right column, last paragraph). Furthermore, the claims of the '515 patent encompass administration of GH analogues and recombinant GH. The person of ordinary skill in the art would have been motivated to make methionyl hGH because Goeddel et al. teach that their recombinant hGH "compares favorably with the expression levels of other cloned genes using the same promoter in optimized conditions" and furthermore that it was produced in large amounts (see p. 548, right column, last 2 paragraphs). For this reason as well, the person of ordinary skill in the art could have reasonably expected success. The teachings of Goeddel et al. indicate that the level of ordinary skill in the art of recombinant production of hGH was high. Furthermore, the instant specification does not contain any objective evidence indicating that methionyl hGH has any surprising qualities with respect to the treatment of Parkinsonism. Thus claim 9 does not contribute anything non-obvious over the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 5, 6, 8-15 and 18, 33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 7,122,515 in view of Bauman (Endocrine Reviews, 1991; 12: 424-449) and further in view of Goeddel et al. (Nature, 1979; 281: 544-548—on Applicants 1449 form filed 7 November 2006. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass methods of administration of GH for any reason, and the claims of U.S. Patent 7,122,515 encompass methods of treating metabolic syndrome comprising administration of GH or an analog thereof or recombinant GH at a dose of about 9.5μk/kg/day, which divided by 1000 (for conversion to mg) and multiplying by 70 (average number of kg of a man) works out to 0.665mg/day, which falls within the range recited in instant claim 18 (see

especially parts (a)-(c)). Claim 1 of the U.S. Patent 7,122,515 recites GH or an analog thereof, therefore is not limited to a type of GH. The reference by Bauman et al. provides evidence of the many types of GH that are implicitly included in the phrase "analog thereof". Regarding instant claim 10, which recites a GH variant lacking the 15 amino acid residues from Glu32 to Glu46 of hGH, instant claim 13, which recites a dimer of human GH, and instant claims 14 and 15, which recite chemically derivatized GH (e.g., deamidated GH), the reference by Bauman provides evidence that these forms are naturally occurring pituitary GH variants (see p. 428, Table 2; and p. 428, whole page through p. 430, left column; see also p. 432, whole page, under "oligomeric GH", which includes as discussion of naturally occurring non-covalent GH dimers). Regarding claims 11 and 12, which recite GH variants lacking the first 8 or 13 amino acid residues at the N-terminus, the reference by Bauman provides evidence that there is a GH variant lacking the first 43 amino acids (GH_{44-191}), which is possibly a native form of GH that has potent diabetogenic activity (see p. 430, right column, last paragraph through p. 431, left column, 1st paragraph). Finally, with regard to claim 9, Goeddel et al. teach about methionyl GH, and how to make it, thus this analog of hGH is also encompassed by the claims of U.S. Patent 7,122,515.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Nishikawa et al. (Protein Engineering, 1989; 3: 49-53) disclose

various analogs of GH and their properties (see abstract; whole document) and Gertler et al. (Endocrinol. 1986; 118: 720-726—on Applicants 1449 form filed 7 November 2006) teach an hGH lacking the first 13 amino acid residues at the N-terminus (see whole document; also abstract), which provides further evidence of the well known GH variants in existence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 9:00am - 3:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest

/Bridget E Bunner/
Primary Examiner, Art Unit 1647